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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/757,824 | 01/09/2001 | Beverly L. Davidson | 875.043US1 | 8235 |

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SCHWEGMAN, LUNDBERG, WOESSNER & KLUTH, P.A.
P.O. BOX 2938
MINNEAPOLIS, MN 55402

| EXAMINER |
|---|
| YAEN, CHRISTOPHER H |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1642 | 11 |

DATE MAILED: 05/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. 09/757,824 | Applicant(s) DAVIDSON ET AL. | |
|---|---|---|---|
| | Examiner Christopher H Yaen | Art Unit 1642 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 April 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-61* is/are pending in the application.

4a) Of the above claim(s) *1-33 and 49-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

1. The examiner of the application has changed. This case has now been transferred as of 4/12/2002. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Christopher Yaen, Group Art Unit 1642.

### *Election/Restrictions*

2. Applicant's election with traverse of Group II in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the restriction is improper and that a search by the examiner of groups I and II would not impose serious burden upon the examiner. This is not found persuasive because the inventions of groups I and II are drawn to two structurally and functionally distinct materials, namely nucleic acids (group I) and polypeptides (group II). These two inventions would pose a burden upon the examiner because two separate searches must be performed and considered. Furthermore, because these two inventions are separated by classification, a restriction requirement is justified. The requirement is still deemed proper and is therefore made **FINAL**.

### *Claim Objections*

3. Claim 38 is objected to because of the following informalities: A period is missing from the sentence. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 34-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. In regards to claims 34 and dependent claims thereof, in the recitation of the phrase *"operatively linked"*, it is unclear as to how a polypeptide is to be operatively linked to a nucleic acid. Clarification is required.

7. In regards to claims 36 and dependent claims thereof, in the recitation of the term *"soiubie"*, it is unclear as to the exact meaning of this term. Are there insoluble forms of an enzyme? Clarification is required.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 34-48 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 34-48 are drawn to a polypeptide comprising a lysosomal enzyme, a naturally secreted protein, a nuclear protein, or a cytoplasmic protein that is operatively linked to a nucleic acid sequence encoding a PTD. The instant specification discloses to one of skill in the art how to make a vector comprising a lysosomal enzyme, namely β-glucorondiase, operatively linked to a PTD, but it is silent with regards to how a polypeptide, in general, is to be linked to a nucleic acid sequence encoding a PTD.

Because the instant specification is silent in this regard, one of skill in the art would be forced into undue experimentation to perform, and use the invention as claimed. The instant application invites the skilled artisan to experiment.

The factors which must be considered in determining undue experimentation are set forth in *In re Wands* 8 USPQ2d 1400. The factors include: (1) quantity of experimentation, (2) the amount of guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the predictability of the art and, (7) breadth of the claims.

With regards to factor one and two cited above, the quantity of experiment required to development and make a polypeptide that is operatively linked to a nucleic acid sequence is high, because the instant specification has not taught one of skill in the art how to make the claimed invention. The instant specification has only taught one of skill in the art how to operatively link a nucleic acid sequence encoding a β-glucoronidase to a nucleic acid encoding a PTD, but it is silent as to how one of skill in the art is to link a polypeptide to a nucleic acid encoding a PTD.

With regards to factors four, five, and six cited above, it is noted that there is a great deal of unpredicatability associated with creating a polypeptide operatively linked to a nucleic acid sequence encoding PTD, or to any nucleic acid sequence, because the art has only taught the creation of vectors or nucleic acid sequences that are operatively linked to other nucleic acid sequences. The instant specification fails to provide specific methodologiocal steps or procedure for which the instant claimed invention can be made or constructed. The art at the time the invention was made, exclusively teaches

the construction of nucleic acid molecules operatively linked to other nucleic acid molecules.

With regards to factors three and seven cited above, it is noted that the working examples are limited to the construction of a expression vector comprising a nucleic acid sequence encoding b-glucoronidase operative linked to a Tat PTD. Such is not seen as sufficient to support the breadth of the claims, wherein the scope of the claims encompasses operatively linking polypeptides to nucleic acid sequences. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art ho to use applicant's alleged discovery, not how to find out how to use it for themselves., see *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

10. The following rejection is based on the examiner's interpretation of claims 34-48 as being drawn to a polypeptide which is expressed when encoded by a nucleic acid encoding for an enzyme, a secreted protein, a nuclear protein, or a cytoplasmic protein, wherein said nucleic acid is operatively linked to a nucleic acid encoding for a PTD, which appears to be the applicant's invention (page 3 **Summary of Invention** section lines 20-31). Claims 34-37, 39-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polypeptide comprising β-glucorinidase, does not reasonably provide enablement for lysosomal enzymes in general, secreted proteins, nuclear proteins, or cytoplasmic proteins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant application, as interpreted by the examiner, is drawn to polypeptides which are expressed when encoded by a nucleic acid encoding for an enzyme, a secreted protein, a nuclear protein, or a cytoplasmic protein of which is operatively linked to a nucleic acid encoding for a PTD. The specification, although enabling for a polypeptide expressed by a β-glucoronidase enzyme nucleic acid, wherein said nucleic acid is operatively linked to a nucleic acid encoding a PTD, is not enabling for any other protein being expressed. Because the instant specification is virtually silent in this regard, the instant invention invites the skilled artisan to experiment.

With regard to factors one and two cited above, the quantity of experimentation required to make, test for functionality, test for effectiveness, and test for proper expression is high because the instant specification has only taught of β-glucoronidase. This is not seen as an adequate amount of guidance in the written description for expressing any polypeptide other than β-glucoronidase.

With regards to factors four, five, and six, it is noted that the instant specification has not provided specific methodological steps, reasons for making, what diseases will be treated for the other proteins claimed in the instant specification. The art at the time has not established with any certainty whether or not the proteins named in the instant application are able to work effectively when operatively linked to PTD.

With regards to factors three and seven, it is noted that the working examples are limited to making and using a polypeptide expressed by a nucleic acid encoding for β-glucoronidase operatively linked to a PTD. Such is not seen as sufficient to support the breadth of the claims wherein the scope of the claims encompasses any lysosomal

enzyme, any secreted protein, any nuclear protein, or any cytoplasmic protein.It is noted that Law requires that the disclosure of an application shall inform those skilled in the art ho to use applicant's alleged discovery, not how to find out how to use it for themselves., see *In re Gardner et al.* 166 USPQ 138 (CCPA 1970).

***Claim Rejections - 35 USC § 103***

11. The following rejection is based on the examiner's interpretation of the claims as being drawn to a polypeptide which is encoded by a nucleic acid encoding β-glucoronidase operatively linked to a PTD encoding nucleic acid.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 34-35,37-38, and 47-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schware *et al.* (Science 1999 Sept 3; 285:1569-1572, **IDS**) in view of Ghodsi *et al.* (Exp Neuro 1999;160:109-116, **IDS** or Hum Gene Therapy 1998 Nov 1; 9:2331-2340, **IDS**). Claims 34-35, 37-38, and 47-48 are drawn to a polypeptide which is encoded by a nucleic acid encoding b-glucoronidase operatively linked to a PTD encoding nucleic acid, wherein the PTD is a TAT, more specifically a $TAT_{47-57}$.

1. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Schware *et al.* disclose of a protein that is operatively linked to a PTD, namely a TAT, and more specifically a $TAT_{47-57}$. Schware *et al.* further disclose that over 50 different proteins have been transduced into cell using this type of PTD domain. Schware *et al.* however do not disclose of β-glucoronidase linked to PTD. Ghodsi *et al.*, however, do disclose of β-glucoronidase, and further discloses of activity and bio-distribution.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make a polypeptide that was operatively linked to a PTD, because the prior art provides sufficient motivation to constructed the invention as claimed. The suggestion/ motivation for doing what the applicant has claimed is that is was already known in the art that proteins that were operatively linked to PTD could be made and used successfully *in vitro* and *in vivo*, as shown by Schware *et al.* Therefore it would have been *prima facie* obvious at the time the invention was made to substitute the protein specifically named in Schware *et al.* with any other protein of choice, and in the instant case a sequence encoding for β-glucoronidase, thus generating a polypeptide that was operatively linked to a PTD. One could expect a reasonable amount of success in accomplishing the claimed invention, because it was already well established in the art that such a protein or polypeptide existed, and with minor modifications, the instantly claimed invention could have been achieved by one of ordinary skill in the art.

***Conclusion***

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1630

Christopher Yaen
Art Unit 1642
May 2, 2002